Secretory Meningiomas: Increased Prevalence of Seizures Secondary to Edema Formation in a Rare Histologic Subtype

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■ OBJECTIVE: **Secretory meningioma (SM) is a rare histologic subtype known to cause disproportional peritumoral brain edema. Although meningiomas are defined by slow growth and mostly manifest with benign clinical symptoms, SMs can cause life-threatening deterioration. The aim of this study was to characterize the potential pitfalls in treatment of SMs by illustrating their characteristic clinical features.**

■ METHODS: **We analyzed 69 patients with SM who underwent surgery at our institution and compared them with a matched nonsecretory meningioma cohort. Retrospective data were analyzed for frequency of seizures as the first presenting symptom, maximum corticosteroid use, intensive care unit stay, and hospital stay. In addition, histologic and radiographic data were evaluated for the extent of peritumoral brain edema formation, tumor location, and tumor size and correlated to clinical presentation.**

■ RESULTS: **Seizures were observed at a significantly higher rate as the first presenting symptom leading to clinical admission in patients with SM (33.3%) compared with the matched nonsecretory meningioma cohort (13%, $P = 0.008$). In patients with SM, seizures were associated with increased edema formation, whereas seizures in patients with nonsecretory meningioma correlated with tumor size ($P = 0.007$). The clinically more complicated course in patients with SM was reflected by increased demand for corticosteroids and a prolonged intensive care unit stay ($P < 0.001$). SM further showed a higher recurrence rate of 35.9% compared with a cohort of 320 World Health Organization grade I meningiomas resected at our institution ($P < 0.001$).**

■ CONCLUSIONS: **Our results illustrate the complicated clinical course of this rare histologic meningioma subtype. The increased frequency of seizures may enable raised awareness of clinicians for potential complications and treatment adjustments perioperatively early at clinical admission.**

INTRODUCTION

Secretory meningiomas (SMs) represent a rare and unique World Health Organization (WHO) grade I histologic subtype of the most common benign intracranial tumor.[1,2] Characterized by periodic acid–Schiff (PAS)–positive hyaline intracellular inclusions, called pseudopsammoma bodies, and glandular-like formations, SMs are known to be associated with disproportionally large peritumoral edema and a complicated clinical course.[3] The extensive brain edema formation, often exceeding the size of the originating tumor, is observed in 13%–64% of all patients with SM.[2-6] Large peritumoral edema in particular is observed in SMs located at the convexity, in tumors with irregular margins, and with absence of a peritumoral rim.[4] Although the growth rate of SM is comparable to the more common meningotheliomatous subtype, the benign histopathologic character of this tumor subtype can be misleading in clinical practice. The space-occupying edema, often resulting in a

Key words
- Complications
- Edema
- Meningioma
- Secretory
- Seizure

Abbreviations and Acronyms
ICU: Intensive care unit
MRI: Magnetic resonance imaging
NS: not significant
PAS: Periodic acid–Schiff
SM: Secretory meningioma
WHO: World Health Organization

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significant midline shift >10 mm, harbors the risk of increased perioperative and intraoperative challenges with potentially life-threatening complications.[3,4] Elevated levels of vascular endothelial growth factor have been suspected to play a major role in vasogenic edema formation.[7,8] However, although 2 SM-specific molecular alterations in the *KLF4* and *TRAF7* genes were discussed more recently using whole-exome sequencing, the pathways and pathophysiologic basis for large edema formation are still unknown.[9] Besides radiographic evaluation, no clinical features are known to predict the potentially complicated intraoperative and postoperative course of SM. Because no clear association between pathophysiology and clinical presentation has been documented, we compared the clinical and radiographic presentation and perioperative management of patients with SM with a matched control cohort of patients with nonsecretory meningioma.

MATERIALS AND METHODS

Patients and Clinical Data

Our analysis included 69 patients with a first presentation of SM and 1 recurrence. Among 1970 meningiomas resected at our department between 1988 and 2015, 69 (3.5%) were histologically diagnosed as SM. Our study extends the patient cohort from Regelsberger et al.[3] and focuses on new clinical aspects. Data from patients with SM were matched to 69 patients with WHO grade I meningioma with nonsecretory histologic subtype. Patient cohorts were matched for age, tumor location, and WHO grade. Clinical and surgical records were retrospectively analyzed for age, sex, symptoms leading to clinical admission, maximum dose of corticosteroids perioperatively, extent of surgical resection, additional therapeutic measures, duration of intensive care unit (ICU) stay, and duration of hospital stay. Corticosteroid use was quantified as maximum milligrams of dexamethasone given preoperatively or postoperatively per day. Seizure as the first symptom leading to clinical admission included clearly focal and generalized convulsive attacks. To allow comparison of the recurrence rate of SMs, 320 WHO grade I primary meningiomas with a normally distributed location and a mean follow-up of 30 months were selected as an institutional control cohort. This larger cohort was chosen to enable an appropriate comparison of the recurrence rate, without limitation in the follow-up time. The statistical analysis was performed using GraphPad Prism 5.0 (GraphPad Software, Inc., La Jolla, California, USA) and applying Fisher exact (χ^2) and Student *t* tests. Completeness of resection was classified using Simpson grading.[10] Analysis of patient data was conducted in accordance with local ethics guidelines.

Histologic Analysis

Histopathologic grading of the samples was performed by 2 neuropathologists according to the 2007 WHO criteria.[11] Samples were formalin-fixed and paraffin-embedded and were stained with hematoxylin-eosin and PAS. Pseudopsammoma density was evaluated semiquantitatively (−, absent; +, few; ++, several; +++, many). Nonsecretory meningioma subtypes included meningiotheliomatous (68.1%), fibrocystic/fibroblastic (13.0%), transitional (11.6%), psammomatous (2.9%), microcystic (2.9%), and angiomatous (1.4%). Additionally, the proliferation index was assessed by immunohistochemical staining for Ki-67 antigen.

Radiologic Data

Images from computed tomography and magnetic resonance imaging (MRI) scans were studied for tumor size and extent of peritumoral edema. Perifocal edema was correlated to tumor size according to Buhl et al.[12] and the modified score by Regelsberger et al.[3] Regelsberger et al. describe edema as follows: grade I, equal to or smaller than tumor size; grade II, surpassing tumor size; and grade III, nearly hemispheric edema. The score by Buhl et al. characterizes edema as follows: "small," smaller than tumor size; "moderate," equal size; and "severe," extending beyond the tumor measurements. Radiographic evaluation was performed by 2 board-certified neurosurgeons. Tumors without connection to the cranial base were classified as non−skull base meningiomas and vice versa. The radiologic data were correlated to histologic subtype and seizure prevalence.

RESULTS

Patients and Clinical Data

The basic and clinical data of all patients are summarized in **Table 1**. Secretory histologic subtype was confirmed in 69 patients. With 1 patient receiving a repeat resection for a recurring mass, 70 tumors were included in the analysis. Patients with SM had a higher female-to-male ratio than the age-matched nonsecretory meningioma cohort (6.7:1 SM vs. 2.5:1 nonsecretory meningioma). The mean age at presentation was 58.5 years in the SM cohort and 58.7 years in the nonsecretory meningioma cohort (range, 35−82 years and 31−86 years). Seizures as first presenting symptom leading to clinical admission were observed in 23 of 69 (33.3%) patients in the SM cohort compared with only 9 (13.0%) patients in the nonsecretory meningioma cohort ($P = 0.0081$) (**Figure 1A**). As demonstrated in **Figure 1** and summarized in **Table 2**, seizures in the SM cohort, but not in the nonsecretory meningioma cohort, correlated to edema formation bigger than the tumor size (defined as Regelsberger grades II and III or Buhl "severe"; $P < 0.001$) (**Figure 1B**), whereas seizure prevalence in the nonsecretory meningioma cohort was significantly associated with tumor size ($P < 0.007$) (**Figure 1C**). First symptoms in the nonsecretory meningioma cohort included headache (26.1%); visual impairment (20.3%); vertigo (15.9%); motor paresis (10.2%); personality changes (4.4%); and others such as anosmia, hyperprolactinemia, and incidental findings (5.8%). Patients with secretory histologic subtype further required higher maximum doses of dexamethasone compared with patients with nonsecretory meningioma (mean ± SEM 15.39 mg ± 1.0 vs. 9.47 mg ± 0.73, $P < 0.0001$) (**Figure 1D**) as well as longer ICU monitoring (mean ± SD 5.73 days ± 9.7 vs. 1.22 days ± 0.70, $P < 0.001$) (**Figure 1E**) and longer hospitalization (mean ± SD 15.41 days ± 9.9 vs. 9.66 days ± 5.0, $P < 0.0010$) (**Figure 1F**). Patients with SM demonstrated a trend toward an increased prevalence of complications during their hospital stay (29.0% vs. 15.9%, not significant [NS]). Furthermore, the frequency of new neurologic deficits at the time of discharge was significantly higher in patients with SM (21.7% vs. 4.4% new deficit, $P = 0.004$). All patients with seizures received anticonvulsive medication only for a short perioperative time.